Evaluate Vantage

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Ardelyx runs into problems with tenapanor

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Hitting the primary endpoint in a pivotal trial is not always the end of a company's problems – just ask Ardelyx. What looked on the surface like a win in the T3MPO-1 trial of tenapanor was overshadowed by seemingly lower efficacy versus rival constipation-predominant irritable bowel syndrome therapies (see tables below).

This, along with a high rate of diarrhoea with tenapanor, spooked investors who sent Ardelyx's stock down 39% on Friday. The company will have to hope that data from its second phase III study in constipation-predominant IBS (IBS-C), T3MPO-2, due in the second half of this year, will allay these concerns.

Down T3MPO

T3MPO-1's primary endpoint was response rate, with response defined as at least a 30% reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements (CSBMs) in the same week for at least six weeks of the 12-week treatment period.

The trial met this but fell short on a key secondary endpoint, the CSBM responder rate.

T3MPO-1 results			
6 of 12 treatment week results	**Tenapanor**	**Placebo**	**P value**
Combined responder (primary endpoint)	27.0%	18.7%	0.02
CSBM responder (increase ≥1 CSBM from baseline)	33.9%	29.4%	0.27
Abdominal pain responder (≥30% abdominal pain reduction)	44.0%	33.1%	0.008

In addition, 15% of patients receiving tenapanor suffered diarrhoea, versus 2% of the placebo group, and the discontinuation rate due to diarrhoea was 6% in the treatment arm.

Tenapanor is not the only IBS-C candidate to be linked with diarrhoea – this is also a common side effect with Allergan and Ironwood's approved therapy, Linzess, which is nevertheless expected to become the best-selling IBS-C treatment by 2022, according to *EvaluatePharma* sellside consensus.

The IBS-C landscape				
Project	**Company**	**Status**	**Mechanism**	**2022e sales ($m)**
Linzess	Allergan/Ironwood	Marketed	Guanylate cyclase type-C receptor agonist	623
Trulance	Synergy Pharmaceuticals	Filed	Guanylate cyclase type-C receptor agonist	244
Tenapanor	Ardelyx	Phase III	Sodium & hydrogen exchanger 3 inhibitor	207
SYN-010	Synthetic Biologics	Phase II	Statin/HMG CoA reductase inhibitor	144
Source: EvaluatePharma.				

Linzess seems to have the edge over tenapanor on efficacy, although the usual caveats about cross-trial comparisons apply. On the same six out of 12 weeks responder endpoint, Ironwood's product showed a 13 and 20-point benefit over placebo in two trials, against the 8-point difference seen in T3MPO-1. And, unlike tenapanor, the Linzess group had a significant improvement in CSBM response versus placebo.

Synergy's Trulance, which in January received FDA approval in chronic idiopathic constipation and is awaiting the go-ahead in IBS-C, also looks slightly better than tenapanor, particularly at the higher dose studied. The project also met the CSBM responder endpoint in a pooled analysis of its two phase III trials.

Phase III results with IBS-C candidates (versus placebo)					
	Linzess		Trulance		Tenapanor
	Trial 1	Trial 2	Study 1	Study 2	T3MPO-1
Combined responder rate	34%	34%	30%	22-24%	27%
Treatment difference	13 points	20 points	12 points	7-10 points	8 points
CSBM responder rate	49%	48%	41-42%*		34%
Treatment difference	19 points	25 points	10-11 points		5 points
Abdominal pain responder rate	50%	49%	37-39%*		44%
Treatment difference	13 points	14 points	10-12 points		11 points
**Pooled analysts; Source: Linzess label, Synergy press release.*					

Importantly, Trulance has a lower incidence of diarrhoea than both of the other candidates, at 4%. Linzess had a diarrhoea rate of 20% in its pivotal trials.

The IBS-C field is looking increasingly competitive and, if Trulance is approved, its side-effect profile could help it take market share from Linzess. Tenapanor, lagging behind on timing, efficacy and adverse events, might have a hard time getting a toehold in the market. If its prospects are to improve, Ardelyx will need better results from T3MPO-2.

Study	Trial ID	Data due
T3MPO-1	NCT02621892	Reported
T3MPO-2	NCT02686138	H2 2017

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